

Management of anaphylactic shock in the operating room

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■ Key points

Diagnosis of anaphylactic shock occurring during anesthesia is challenging because of altered clinical signs and confounding diagnoses (e.g. arterial hypotension).

A major sign of clinical severity in the presence of arterial hypotension is a low end-tidal CO₂ concentration (below 20 mmHg).

Acute hemoconcentration (increase of hemoglobin concentrations) is highly suggestive of vascular leak triggered by anaphylactic shock.

Guidelines for management of anaphylactic shock occurring during anesthesia are based on withdrawal of the suspected allergen, airway control, increased cardiac preload by the Trendelenburg position and volume expansion, epinephrine, glucocorticoids and monitoring for 24 hours, although evidence for the efficacy of these therapeutic interventions is absent or very weak.

Refractory anaphylactic shock although not defined could be characterized by persistent clinical signs after more than 10 minutes of adequately managed resuscitation. It should trigger enhanced cardiac monitoring through echocardiography to detect primary myocardial dysfunction and alert for extracorporeal life support.

Drugs that may be used for refractory anaphylactic shock in addition to epinephrine are glucagon, norepinephrine, vasopressin, methylene blue but there are only animal studies where these drugs were compared to epinephrine.

Follow-up after resuscitation includes patient information on the drugs given before occurrence of clinical signs, scheduled allergology investigation, pharmacovigilance report and recovery of the conclusions of allergology investigation with clear decisions on the identification of the culprit agent and subsequent avoidance. All these conclusions have to be traced in the medical record and shared with the patient.

■ Points essentiels

Prise en charge du choc anaphylactique au bloc opératoire

Le diagnostic clinique de choc anaphylactique per-anesthésique peut être difficile à poser, du fait de l'atténuation des signes cliniques ainsi que de l'importante incidence des diagnostics différentiels (comme l'hypotension artérielle).

L'un des principaux signes de gravité clinique en association avec une hypotension artérielle est une diminution de la fraction expirée de CO₂ (inférieure à 20 mmHg).

L'hémoconcentration aiguë (élévation de l'hémoglobémie) est hautement suggestive d'une fuite capillaire induite par le choc anaphylactique.

Les recommandations pour la prise en charge du choc anaphylactique pendant une anesthésie reposent sur le retrait de l'allergène suspecté, le contrôle des voies aériennes supérieures, l'élévation de la précharge par la position de Trendelenbourg et l'expansion volémique, l'adrénaline, les glucocorticoïdes et le monitoring pendant 24 heures.

En absence de définition précise, le diagnostic de choc anaphylactique réfractaire peut être évoqué devant la persistance des signes cliniques 10 minutes après l'initiation de thérapeutiques selon les recommandations. Cela doit inciter au monitoring de la fonction cardiaque par échocardiographie afin de détecter des dysfonctions primaires et d'alerter les équipes d'assistance circulatoire.

Bien que basées sur des études réalisées chez l'animal, les alternatives thérapeutiques à l'adrénaline lors d'un choc anaphylactique réfractaire sont le glucagon, la noradrénaline, la vasopressine et le bleu de méthylène.

Après la réanimation, le suivi du patient doit comprendre l'information du patient sur les médicaments possiblement incriminés, la date du rendez-vous d'allergo-anesthésie, la signalisation de l'évènement à la pharmacovigilance ainsi que la récupération des résultats des investigations allergologiques avec les conclusions claires sur l'agent responsable et les conduites à tenir. Ces résultats doivent être notifiés dans le dossier médical du patient.

Definition

Anaphylaxis has been defined in 2006 as "a serious allergic reaction that is rapid in onset and may cause death" [1]. The clinical criteria for diagnosing anaphylaxis have been recently revised (*table I*). The severity of anaphylactic reactions can vary

from minor to death as classified by Ring and Messmer in 1977 (*table II*) [2]. The occurrence of an anaphylactic reaction during anesthesia increases the diagnostic difficulties because of:

- the absence of some clinical signs, such as anxiety, dyspnea, abdominal pain;
- the impossibility to detect existing signs (erythema) if surgical dressing covers the patient;
- major signs of anaphylactic shock (AS) (e.g. arterial hypotension, tachycardia) can have many other causes during anesthesia and surgery;
- anesthesia per se alters the compensatory mechanisms that an awake individual would mobilize during an anaphylactic reaction.

This could explain the much higher fatality rate of AS during anesthesia (4.1%) [3], as compared to that of patients admitted to emergency departments for anaphylaxis (approximately 0.7/million population) [4].

The specificities of anaphylaxis/AS during anesthesia and surgery, the object of this article, are related to the fact that within minutes, the anesthesiologist must recognize signs of anaphylaxis that can also much more frequently occur because of other causes (e.g. arterial hypotension), evaluate the severity of these

Glossary

ACLS	advanced cardiovascular life support
AS	anaphylactic shock
ECLS	extracorporeal life support
ECPR	extracorporeal cardiopulmonary resuscitation
EDRF	endothelium-derived relaxing factor
etCO ₂	end-tidal CO ₂
Ig	immunoglobulin
IV	intravenous
LV	LEFT Ventricular
NMBA	neuromuscular blocking agent
NO	nitric oxide
PAF	platelet activating factor
PHT	pulmonary hypertension
SVR	systemic vascular resistance

TABLE I

Clinical criteria for diagnosing anaphylaxis [1]

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following

Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours)

Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

Reduced BP after exposure to known allergen for that patient (minutes to several hours)

Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP¹

Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

PEF: peak expiratory flow; BP: blood pressure.

¹Low systolic BP for children is defined as less than 70 mmHg until 1 year, less than 70 mmHg from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

TABLE II

Severity scale of anaphylactic shock, according to the Ring and Messmer classification [2]

Grade	Symptoms
I	Skin symptoms: erythema, urticaria localized or extended with or without angioedema
II	Moderated organ failure: arterial hypotension, tachycardia, cough, dyspnea, wheezing, digestive troubles (nausea, vomiting, diarrhea)
III	Severe organ failure: hemodynamic collapse, cardiac arrhythmia, bronchospasm, severe digestive signs
IV	Cardiac or respiratory arrest

reactions, make differential and positive diagnosis, identify the possible allergen (based on epidemiology and the chronology of suspected allergen administration for that patient), initiate therapy, titrate it in order to avoid severe side effects (e.g. for catecholamines), evaluate the efficacy (or lack) of therapy and initiate the positive diagnostic approach. In cases of refractory AS or cardiac arrest, last resort rescue measures such as extracorporeal life support (ECLS) must be rapidly initiated. Finally, a major challenge is the fact that the evidence for all therapeutic measures recommended in AS (epinephrine, histamine receptors antagonists, glucocorticoids) is absent or very weak (see for a review [5]).

The purposes of this article are:

- to review the pathophysiology of AS with a focus on the clinical signs and therapeutic decisions (as opposed to mediators and mechanisms that are only helpful a posteriori but not during the resuscitation of AS);
- to briefly review the international guidelines on therapy of AS occurring during anesthesia and surgery;

- to provide a Diagnostic and Therapeutic Pathway Checklist that could be helpful upon occurrence of AS.

Epidemiology of AS occurring during anesthesia and surgery

Globally, the incidence of allergy is increasing worldwide with the lifetime risk of anaphylaxis being at least 1.6% [4]. The incidence of perioperative anaphylaxis is estimated between 1/10,000 and 1/20,000 anesthesia procedures [6]. Translated to individual practice when performing 1500 anesthetic procedures a year, an anesthesiologist has a probability of seeing a case of severe anaphylaxis in his/her practice every 5–10 years. Acquisition and preservation of clinical skills for such rare events is challenging. For comparison, the incidence of severe arterial hypotension (defined as a decrease of more than 50% of systolic/mean arterial pressure) occurs in approximately 5–10% of anesthetic procedures. These major differences in incidence may explain the delayed diagnosis of AS during anesthesia.

The most frequent allergens responsible for AS during anesthesia are neuromuscular blocking agents (NMBA) (40–60% of the cases) followed by latex (20%), antibiotics (18%), opioids/colloids (2–3%) and hypnotics (1%) [7,8]. Chlorhexidine is also increasingly recognized as an allergen [9]. These epidemiology data are important when attempting to identify the possible allergen.

Among the NMBA, suxamethonium is the most frequently incriminated (61%), followed by atracurium (20%), cis-atracurium (6%), vecuronium (5%) and rocuronium (4%) (proportion in consideration of the market share) [7]. Cross-reactivity between NMBAs is observed in 50–75% of the cases, mostly with the steroids drugs. A large number of AS related to NMBA occurred in patients who had never been previously exposed to NMBA (previous exposure being most frequently suspected based on a history of surgical/anesthetic procedures). Substituted ions ammoniums have long been considered as the most likely epitope for the binding of specific immunoglobulin E. The main hypothesis for the sensitization is the exposure to compound with a tertiary or quaternary ammonium, such as cough syrup with pholcodine [10], cosmetics, household products, disinfectants, food or industrial materials [11]. The important message from this information is that first time exposure to an allergen (because of cross-reactivity) is consistent with the diagnosis of AS.

Physiopathology

In humans, the predominant organs affected by life threatening anaphylaxis are the respiratory and the cardiovascular systems [12]. For those reasons, anaphylaxis might be particularly severe in patients with underlying cardiovascular diseases, although the presence of profound myocardial depression has also been described in healthy patients [13,14].

Cardiac anaphylaxis

"Cardiac anaphylaxis" is a term not properly defined in the literature. It may refer either to:

- the mainly or isolated cardiac manifestations of anaphylaxis without the other cardinal signs;
- documented transient or persistent alteration of myocardial systolic function (several cases of allergy to protamine have revealed acute right ventricular failure secondary to highly increased pulmonary vascular resistance attributed to platelet activating factor [PAF]) [15];
- severe cardiac complications (e.g. myocardial infarction, refractory cardiac arrest) following AS and resuscitation with epinephrine.

Classical or reverse Takotsubo syndromes have been reported after resuscitation of AS [16,17].

The Kounis syndrome refers to allergy-associated acute coronary syndrome [18]. Type I is a vasospasm in healthy coronary arteries; type II a destabilization of a previously present coronary

atheroma plaque; type III an intrastent thrombosis [18,19]. Anaphylaxis mediators can either trigger cardiac complications (as suggested by Kounis) or reveal subclinical cardiac pathologies. The weight of evidence is that anaphylaxis reveals subclinical cardiac diseases. This could explain why patients with documented cardiac diseases are at increased risk of death upon occurrence of AS [3]. Whatever the mechanisms, myocardial damages detected by increased cardiac troponin concentrations have been reported [18]. There is convincing evidence that cardiac manifestations of AS are not limited to Kounis syndrome and this is why we prefer the term "cardiac anaphylaxis".

Low cardiac output during AS related to decreased preload

Classically, AS presents as partially and rapidly overlapping pathophysiological mechanisms [20]. Initially a distributive shock, characterized by reduced systemic vascular resistance (SVR), low left ventricular (LV) afterload and tachycardia can be observed although this may be very transient. Secondly, volume loss due to increased capillary permeability decreases venous return and cardiac flow, corresponding to a hypovolemic shock. In this case, the heart should be "empty".

Other mechanisms of low cardiac output during AS

Alteration of the systolic/diastolic myocardial function

Alteration of the systolic/diastolic myocardial function, either from the onset of AS or following initiation of its therapy, could occur, even in healthy hearts through several mechanisms (figure 1):

- epicardial coronary vasospasm secondary to cardiac mast cells degranulation (histamine in patients with vasospastic angina [21], prostaglandin D2 [PGD2], angiotensin II, leukotriens) with subsequent myocardial ischemia;
- a direct negative inotropic effects of some mediators (lipid mediators such as leukotrienes or prostaglandins [22,23]);
- secondary to treatment (epinephrine, other vasoconstrictors) either by coronary vasoconstriction or increased myocardial oxygen consumption.

It is probable that in patients with previous cardiac diseases, the presence of an increased number of mast cells within the cardiac tissue [24] increases both the concentrations of mediators within the myocardial tissue and the consequences of their secretion as well as lower the tolerance to arterial hypotension and treatment of AS.

Pulmonary hypertension and right ventricular failure

The major model for this presentation is the AS induced by protamine, which incidence is around 0.19% [25]. The most common factor predisposing to an anaphylactic reaction to protamine sulfate is prior treatment with neutral protamine hagedorn. Protamine sulfate is used in order to reverse the anticoagulant effects of heparin, mainly after bypass for cardiac surgery. Protamine has major systemic side effects: drop of SVR leading to hypotension, increased myocardial oxygen

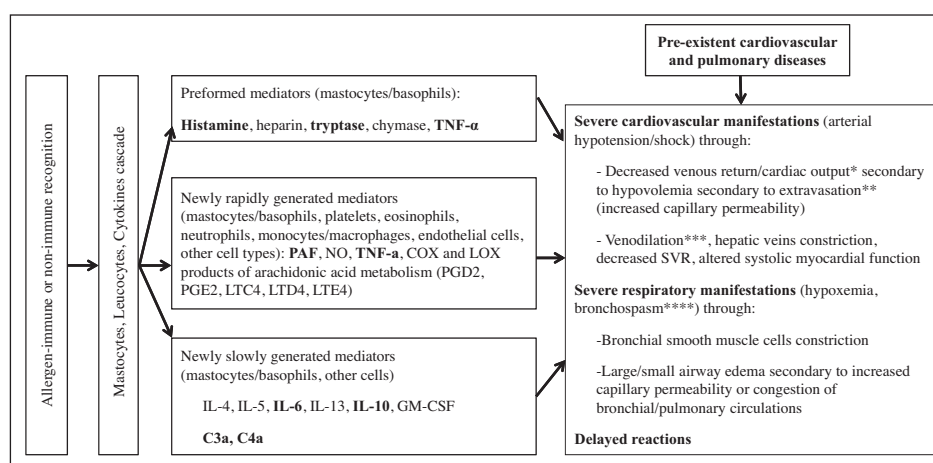


FIGURE 1

Simplified diagram of the cell types and non-cellular mediators involved in the clinical manifestations of severe forms of anaphylaxis

The main mechanisms of cardiovascular and respiratory manifestations of severe forms of anaphylaxis documented in humans (and also of delayed reactions) are statistically related (although not causally demonstrated) to the mediators in bold characters (modified from [60]). Pathophysiologic mechanisms and mediators described in animal models but not documented in humans are not represented. Signs that can facilitate diagnosis: *: decreased end-tidal CO₂; **: hemoconcentration as attested by acutely increased hemoglobin values; ***: decreased cardiac filling pressures except in patients with pre-existent cardiac disease; ****: increased airway pressure values. Abbreviations: TNF- α : tumor necrosis factor alpha; PAF: platelet activating factors; NO: nitric oxide; COX: cyclooxygenase; LOX: lipoxygenase; PG: prostaglandin; LT: leukotriens; IL: interleukin; GM-CSF: granulocyte/monocyte cell stem factor; C3a/C4a: respective complement fraction.

consumption, cardiac output, and heart rate. It can also lead to catastrophic pulmonary vasoconstriction and be responsible for anaphylactoid reactions [15]. Protamine is a major vasodilator agent, through the activation of the endothelium-derived relaxing factor (EDRF)/nitric oxide (NO) (EDRF/NO). The major hypothesis to the pulmonary vasoconstriction induced by histamine is the release of thromboxane or others constrictive autoids in individuals who lose the ability of releasing EDRF/NO in the pulmonary circulation because of pre-existent lesions or reperfusion lesion in the pulmonary endothelium, which induces catastrophic pulmonary vasoconstriction and pulmonary hypertension (PHT) [15]. Severe PHT leads very quickly to right ventricular failure, which requires an immediate treatment.

Evaluation of fluid loss

There are few pathognomonic signs of anaphylaxis. In this context, one could assert that acute hemoconcentration as assessed by the increase concentration of hemoglobin (in the absence of acute diuresis) is highly suggestive of the occurrence of anaphylaxis (and vascular leak). Consequently, correction of hemoconcentration may attest the efficacy of volume expansion. This has been demonstrated by our group in an animal study [26].

Altered cerebral blood flow

Whereas cerebral blood flow is conserved during pharmacologically-induced arterial hypotension, one study showed a linear relationship between cerebral cortical blood flow and blood pressure during hypotension in AS in a rat model [27]. AS

resulted in severe impairment of cerebral blood flow and oxygenation, beyond what could be expected from the level of arterial hypotension. It was also demonstrated that for comparable effects on correction of arterial hypotension, the use of epinephrine was associated with better brain oxygenation (at least initially) as compared to the use of arginine vasopressin. This was interpreted as potentially related to the beta2-adrenergic vasodilatory cerebral effect of epinephrine [28]. These observations probably reflect the specific pathophysiology of AS and suggest that therapeutic goals during AS may go beyond correction of severe arterial hypotension especially in patients with pre-existent alterations of cerebral circulation reserve (i.e. stenosis on cerebral arteries).

Other clinical signs (bronchospasm or digestive signs)

One of the ways of performing differential/positive diagnoses of AS is to interpret the clinical signs by taking into account the patient's medical history. In this context, our group has investigated the hypothesis that a documented history of asthma (past or active) could be associated with an increased probability of having bronchospasm occurring during AS [29]. Such a hypothesis would have credibility based on the common mechanisms that underlie asthma and bronchospasm during anaphylaxis. During AS with a hemodynamic component, this associations does not exist and this probably reflects the complexity of bronchospasm (congestion of the bronchial wall) as a predominant mechanism [29]. Persistent gastrointestinal symptoms

(e.g., crampy abdominal pain, vomiting) are criteria of anaphylaxis, as defined by [30]. Under anesthesia, patients can not report them. However, vomiting might be a sign of severity, as related to the drop of arterial blood pressure.

Consequences for clinical practice

In clinical practice, many of the cardiac risk factors may be unknown and therefore the relevant messages are as follows:

- isolated/predominant cardiac signs (arrhythmia, ST segment modifications, hemodynamic signs of altered systolic function, echocardiographically-documented alteration of systolic function or increased cardiac troponin concentrations) can be the only/major manifestation of anaphylaxis;
- in a clinically "complete" picture of anaphylaxis, inefficient therapy with the classical regimen (volume loading, epinephrine) may be explained by myocardial contractile dysfunction or increased right ventricle afterload and this must be documented by echocardiography (either transthoracic or transoesophageal);
- the documentation of severe myocardial dysfunction or refractory cardiac arrest should be treated promptly with ECLS, although this technique is still controversial [3], at least in hospitals that perform cardiothoracic surgical procedures.

Occurrence of cardiac complications during/after AS must also trigger post-event investigations to find a previously undiagnosed cardiac disease (the most frequent being coronary atheroma given the present of mast cells in the atheroma plaque) [31].

International guidelines for the treatment of anaphylactic shock

The American Heart Association and the French society of anesthesiology and intensive care published recommendations about the treatment of AS [5,32–34]. The most difficult issue before initiating treatment is recognition of AS as the cause of the alteration of cardiovascular/respiratory functions. There are several clues to early recognition of AS:

- the concomitant occurrence of skin, however inconstant, cardiovascular and respiratory signs minutes after infusion of a substance documented to provoke AS;
- the presence of arterial hypotension and very low concentrations of end-tidal CO₂ (etCO₂).

Although there are no specific prospective data on this topic, values below 20 mmHg just after insertion of tracheal tube with a plateau (that are the proof of acceptable bronchial permeability) are major signs of the severity of arterial hypotension related to the decrease in cardiac output. We proposed a diagnostic and treatment pathway checklist for AS, inspired by the model from trauma resuscitation (table III).

Every patient with suspected AS has to be closely monitored. The first step is to retrieve the suspected agent immediately. Direct antagonisation (through chemical interactions) has been described for protamine anaphylaxis with heparin being able to

create complexes with protamine. Reports on rocuronium AS withdrawn with sugammadex are controversial [35].

After having informed the surgical and anesthesia teams and increased the inspired oxygen fraction to 1, the specific treatment will be guided by the severity of the reaction (table II). In grade I reaction, these actions might be enough. Whatever grade is considered, the use of H₂-antihistamines is not based on solid evidence [5]. Although there are no human trials establishing the role of epinephrine or preferred route of administration in AS [5], epinephrine should be administered in grade II or III by intravenous (IV) bolus infusion every 1 or 2 minutes of 10 µg or 100 µg respectively, until mean arterial pressure is higher than 60 mmHg. A continuous IV infusion of epinephrine at 0.05–0.1 µg/kg/min might be useful and should be started immediately in severe forms. Pathophysiologic arguments favor the continuous infusion because of the modulatory effects of epinephrine on the release of mediators. Intramuscular administration is also possible (0.2 to 0.5 mg), preferably in the vastus lateralis muscle if accessible and should be repeated every 5–10 minutes in the absence of clinical improvement (i.e. correction of arterial hypotension). Aggressive fluid resuscitation with crystalloids has to be continued to counter the vasogenic shock until hemodynamic stability [32,33]. Volume loss can concern up to 70% of the blood volume [36]. As colloids have been shown to be more effective than crystalloids in a rat model [37], colloids could be useful if the cumulative volume of crystalloids is above 30 mL/kg. If a colloid was already infused before the occurrence of signs of AS, that type of colloids should not be used for resuscitation of AS, because it has to be considered as a potential allergen. For patients under β-blockers, epinephrine may need to be increased (first IV bolus of 100 µg followed by bolus of 1 to 5 mg every 1–2 minutes). Glucagon could be proposed (1–2 mg IV every 5 minutes, and if necessary continuous infusion of 5–15 µg/min or 0.3–1 mg/h).

In severe forms, advanced airway management should not be delayed (if not already secured) and might need endotracheal intubation, given the potential for the rapid development of oropharyngeal or laryngeal edema. Beta2-adrenergic agonists, such as salbutamol, relieve bronchospasm (but not upper airway obstruction or shock). They could be delivered by inhalation or IV in case of severe form (bolus of 100–200 µg and, if necessary, continuous IV infusion of 5–25 µg/min). However, the intravenous administration should be avoided in case of hypotension because it may increase the severity of the shock.

Grade IV anaphylaxis reaction, i.e. cardiac arrest secondary to anaphylaxis, should be treated with standard advanced cardiovascular life support (ACLS): upper airway management, mechanical ventilation, cardiopulmonary resuscitation/chest compression, fluid challenge, epinephrine by IV bolus (1 mg every 1–2 minutes) and infusion.

Corticosteroids (hydrocortisone 200 mg every 6 hours) are used to decrease the late manifestations of anaphylaxis but the

TABLE III

Diagnostic and treatment pathway checklist for anaphylactic shock (issued from the model from trauma resuscitation)

	Yes	No	N/A	Reasons for variance
Initial diagnostic phase				
Several clinical signs consistent with AS	☐	☐	☐	
Suspected substance identified and stopped	☐	☐	☐	
Severity (grade) of AS according to severity defined	☐	☐	☐	
Initial therapy				
Time count initiated from the first signs	☐	☐	☐	
Airway control and FiO ₂ = 1	☐	☐	☐	
Volume expansion initiated	☐	☐	☐	
Trendelenbourg position or other (e.g. pregnant patient)	☐	☐	☐	
Injection of epinephrine titrated on initial severity of hemodynamic alterations and response to therapy	☐	☐	☐	
Bronchodilator given and adjustment of ventilation to avoid hypoventilation/hypercapnia if severe bronchospasm	☐	☐	☐	
ACLS initiated if cardiac arrest recognized	☐	☐	☐	
Histamine receptors antagonists	☐	☐	☐	
Corticoids	☐	☐	☐	
Consider antagonist (e.g. heparin for protamine, sugammadex for rocuronium)	☐	☐	☐	
After 10 minutes from start of resuscitation, consider diagnosis of refractory anaphylactic shock				
Consider echocardiography	☐	☐	☐	
Consider alerting the ECLS team	☐	☐	☐	
Decisions on the procedure for which the patient was anaesthetized	☐	☐	☐	
Blood samples for histamine, tryptase and other laboratory measurements	☐	☐	☐	
Second line measures (first 24 h)				
Monitoring in ICU/PACU for 24 hours	☐	☐	☐	
Subsequent blood samples	☐	☐	☐	
Documents provided to the patient concerning suspected drugs/substances until the allergy investigation confirms it	☐	☐	☐	
Events/therapy traced in the medical/anaesthesia files	☐	☐	☐	
Allergology follow-up visit scheduled	☐	☐	☐	
Pharmacovigilance report	☐	☐	☐	
Results of allergology investigation obtained	☐	☐	☐	
Results traced in the medical/anaesthesia records and recommendations for future anesthesia traced	☐	☐	☐	
Patient informed on the decisions/diagnosis. Card and recommendations provided in a written document to the patient	☐	☐	☐	

AS: anaphylactic shock; ECLS: extracorporeal life support; ICU/PACU: intensive/peri-anesthesiology care unit.

evidence base is absent [5]. After recovery, a close monitoring has to be maintained during 24 hours, because of the risk of a second late manifestation (bi-phasic evolution).

Refractory anaphylactic shock

There are no universally accepted definitions of refractory AS [38]. In the literature, lack of effect of as little as 100 µg of epinephrine is diagnosed as refractory AS. From the point of view of timing of resuscitation, more than 10 minutes of adequately managed resuscitation (volume expansion, more than 1 mg of epinephrine) [39] could be the trigger to initiate

transoesophageal echocardiography (see previous discussion of "cardiac anaphylaxis"), potential use of alternatives to epinephrine and to initiate the alerts on the ECLS teams given the fact that even when ECLS is available in an institution, it requires a minimum of 20 minutes before insertion and effective cardiovascular support.

Vasopressin

Arginine vasopressin is a potent vasoconstricting substance that has been in the focus of interest in the treatment of cardiac arrest during several years. It has been integrated into the ACLS

resuscitation guidelines as an alternative vasopressive agent in the treatment of cardiac arrest. It has also been reported for treating catecholamine resistant hypotension during cardiopulmonary bypass and septic shock [40]. Moreover, it has been suggested that vasopressin enhances the effects of α -adrenergic stimulation in animals and human both in vitro and in vivo [41]. In an experimental setting, Tsuda et al. demonstrated that the addition of vasopressin to epinephrine reverses histamine-induced vasodilatation of human internal mammary arteries [42]. The hypothesis is that epinephrine only partially reverses histamine-induced vasodilatation, whereas vasopressin, methylene blue, and drugs involved in the inhibition of NO and prostaglandin generation lead to a complete reversal of the vascular relaxation [42].

Vasopressin has been successfully used in few patients with anaphylaxis (with or without cardiac arrest): cardiac arrest after insects' stings [43], refractory hypotension to phenylephrine after aprotinin anaphylaxis during cardiac surgery [44], several surgeries [45-47]. Doses reported were very different in those studies, from 2 IU IV to 40 IU plus infusion. In animal models, vasopressin has similar systemic effects than epinephrine but delays restoration of cerebral tissue oxygen pressure as compared to epinephrine [27,28]. The clinical consequences of these results are not known but underline the importance of taking into consideration regional circulations when assessing the efficacy of vasoconstrictors used in the resuscitation of AS.

Methylene blue

Methylene blue has been proposed during AS as it blocks accumulation of cGMP (guanylate monophosphate) by competitively inhibiting the enzyme guanylate cyclase. Methylene blue increases SVR and reverses shock in animal models [15,48]. In the previous experimental study of Tsuda et al. reported, methylene blue, L-NMA, and indomethacin were only partially effective [42], suggesting that they may offer a potential complementarily therapeutic option in the treatment of histamine-induced vasodilatory shock. It has indeed been reported in numerous cases of vasoplegia after cardiac surgery and cardiopulmonary bypass [49-51]. Some reports provide descriptions of severe refractory anaphylaxis, in which the use of methylene blue was associated with a significant clinical response [15,48,52,53]. In a rat model, the association of methylene blue to epinephrine was the best treatment to restore hemodynamic stability and to prevent brain ischemia [38].

Other alpha-agonists

For refractory hemodynamic shock or cardiac arrest to epinephrine, norepinephrine, terlipressin, metaraminol, or methoxamine may be considered [5]. No randomized controlled trials have evaluated epinephrine versus the use of those drugs for cardiac arrest due to anaphylaxis.

Extracorporeal life support

In case of refractory cardiac arrest, ECLS must be considered as it delivers the best cardiac flow, myocardial perfusion and aortic pressure. Even in the absence of sufficient evidence of extracorporeal cardiopulmonary resuscitation efficacy for patients with cardiac arrest, the American Heart Association guidelines update for cardiopulmonary resuscitation considered the possibility of extracorporeal cardiopulmonary resuscitation during cardiac arrest, but only in cases where it can be rapidly implemented and for select patients with a reversible suspected etiology of the cardiac arrest [54].

ECLS has been successful in isolated case reports of refractory AS to conventional treatment before cardiac surgery [55], cholecystectomy [56], liver transplantation [57] or during coronary intervention [58]. It has also been reported in an Australian series of 23 patients in charge for cardiac surgery, all of whom (except one) recovered successfully from surgery after the instauration of ECLS [59]. Its efficacy in this indication is still under discussion [3], explaining that use of these advanced techniques may only be considered in clinical situations where the required professional skills and equipment are immediately available.

Conclusion

Perioperative AS is life threatening with a mortality rate of 4.1%. Thus, although it may be challenging because of altered signs, an early diagnosis of AS is essential to recognize clinical severity signs and to initiate therapy. The cardiovascular system is one of the predominant organ affected by a perioperative AS. Whatever mechanisms are involved, this explains why the time frame of the AS can be so quick and dramatic for the evolution of the patient, moreover when associated with decreased cerebral blood flow and bronchospasm. Recommended treatments are mainly based on retrieval of the culprit agent, epinephrine and volume expansion. Others treatment, such as vasopressin, methylene blue or ECLS, need to be also considered and would benefit from multicentric studies. Thanks to better knowledge of pathophysiology of AS from animal models and in humans, some specific treatment targeted against the mediators involved such as PAF might also be of interest in few years. none.

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